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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,758	03/24/2004	Daniel J. Von Seggern	5410-006 (312552-24)	6593

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
03/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,758	SEGGERN, DANIEL J. VON	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,14,16,18-22 and 25-52* is/are pending in the application.

4a) Of the above claim(s) *5,18-22,29-33 and 41-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-8, 14, 16, 25-28 and 49-52* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/3/2010 has been entered.

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 5, 18-22, 29-33 and 41-48, drawn to an invention and a specie nonelected with traverse in the reply filed on 7/2/08 & 11/7/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-4, 6-9, 14, 16, 25-28, 34-40 and 49-52 are examined on the merits. Claims 49-52 are new.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 2/25/2010 was filed after the mailing date of the final Office action on 9/3/2009. The submission is in

compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Applicant's arguments filed 2/3/2010 have been fully considered but they are not persuasive. See responses below.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(New Rejection) Claims 37-40 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Since the claimed invention is only drawn to "A cell…" [See claim 37], the claimed invention is interpreted as a product of nature. By amending the claims to recite, "An isolated cell..." this rejection can be overcome.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(New Rejection Necessitated by Amendments) Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a New Matter rejection.

The terms "KO1" and "KO12" as recited in claim 49 with regard to being modifications associated with reduced interaction between the fiber and HSP (see claim 6) are not supported by the original disclosure or claim as filed.

Applicant's amendment, filed 2/3/2010, points to paragraphs 115 and 116 and Example 1 of the published version of the instant application, and asserts that no new matter has been added.

However, the specification as filed does not provide sufficient written description of the above-mentioned limitations. The specification does not provide sufficient support for KO1 or KO12 modifications being associated with reduced interaction with HSP by the viral fiber protein. Moreover, the specification specifically discloses that such modifications are associated with CAR interaction of the fiber protein (see page 22 of the specification). Therefore, the claims represent a departure from the specification and claims as originally filed.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. §112.

Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP §714.02, §2163.05-06 and §2173.05(i).

(Prior Rejection Maintained) Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. Claim 28 recites, "A composition of claim 26 wherein the composition is formulated as a vaccine for stimulating CD8+ T cells in the subject. However, it is unclear what this vaccine is directed towards since no additional limitations are claimed. The metes and bounds of the claims cannot be determined without further clarification.

Even though applicants have amended claim 28 with "for stimulating CD8+ T cells in the subject", the claim remains to be unclear about what is being targeted by the vaccine.

Claim Rejections - 35 USC § 103

(New Rejection Necessitated by Amendments) Claims 1-4, 6, 8, 14, 16, 25-27, 34-40, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shankara (WO 99/47180), Dechecchi et al. (Journal of Virology, 2001) and Huang et al. (Journal of Virology, 1999).

The claimed invention is drawn to an adenovirus particle with a heterologous fiber or a portion thereof, whereby binding of the viral particle to dendritic cells is increased compared to a particle that expresses native fiber proteins. The adenovirus particle is Ad5 adenovirus (a subgroup C adenovirus) with the fiber comprising a sufficient portion from adenovirus 37 (a subgroup D adenovirus) that targets dendritic cells. The fiber can be chimeric with the N-terminus portion from a subgroup C adenovirus which is sufficient to increase incorporation into the particle in comparison to its absence in the fiber protein; or when the 15, 16 or 17 N-terminal amino acids of the Ad37 fiber are replaced with 15, 16 or 17 N-terminal amino acids of an Ad5 fiber; or the fiber is wholly from Ad37, which imparts a reduced interaction with HSP. The

recombinant adenovirus particle is formulated for administration via intramuscular, IV or parenteral routes. The claimed invention also includes an adenovirus vector that encodes this recombinant adenovirus particle, which includes heterologous nucleic acids and dendritic cells that contain these nucleic acid molecules. The fiber can also be modified to reduce any interaction with heparin sulfate proteoglycans (HSP). In addition, the heterologous nucleic acid encodes a product that alters the dendritic cell activity and the heterologous nucleic acid can encode a tumor antigen.

Shankara teaches the generation of a recombinant Ad2 (a subgroup C adenovirus) with a heterologous fiber protein or a chimeric fiber protein with heterologous portions from Ad17 (a subgroup D adenovirus). Shankara teaches that upon replacing all of the Ad2 fiber protein except for the first 16 N-terminal amino acids with the complementing regions of Ad17 fiber proteins, dendritic cell targeting increased greater than 10 fold. (Table 2). This increased targeting was confirmed by the heterologous gene of βgal that altered the activity of dendritic cells in order for the expression of the protein of the gene. As a result, Shankara suggests that the fiber of subgroup D adenoviruses permits the targeting of dendritic cells. Shankara also teaches the development of recombinant Adenovirus 5 with a heterologous fiber protein from Adenovirus 2. Shankara also suggests that recombinant adenoviruses can be formulated in such a way to facilitate administration via intramuscular routes. The chimeric adenoviruses taught by Shankara are capable of also containing nucleic acids that encode for tumor antigens. However, Shankara does not teach the use of Ad37 fiber protein segments; or the lack of HSP interaction by the recombinant adenovirus. *See pages 6, 7, 26.*

Dechecchi et al. teach the involvement of adenovirus 2 and 5 fibers for infecting cells that contain heparin sulfate glycoaminoglycans (components of HSP). Therefore, changes made to these proteins or their replacement could alter binding to HSP. *See page 8772.*

Huang et al. teach the generation of recombinant Ad37 fiber proteins for determining how amino acid mutations can alter the cellular tropism of the fiber protein. *See pages 2798 and 2799.*

It would have been obvious to one of ordinary skill in the art to modify the composition taught by Shankara in order to create a recombinant Ad5 with a fiber protein containing either all or a portion of the fiber protein from Ad37, thereby targeting dendritic cells and generating a recombinant adenovirus with a fiber protein that has a reduced interaction with HSP. One would have been motivated to do so, given the suggestion by Shankara that Ad2 (a C adenovirus) with a fiber protein from Ad17 (a D adenovirus) increases the targeting of dendritic cells. There would have been a reasonable expectation of success, given the knowledge that adenoviruses 2 and 5 use their fiber protein to interact with cellular HSP during infection, as taught by Dechecchi et al., and also given the knowledge that mutating Ad37 fiber protein in order to determine the affect mutations have on cellular tropism, as taught by Huang et al. Furthermore, while Shankara and Huang et al. do not comment on reduced HSP interaction, this would have been a natural outcome of combining their teachings as outlined above, particularly in view of Dechecchi et al. In addition, the structure of the product is the same as is instantly claimed, thus any function(s) associated with the claimed structure is expected to be present in the structure of the prior art. Thus the

invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments:

Applicants argue that while Shankara teach one chimeric adenovirus had an increased targeting of dendritic cells, other chimeric adenoviruses had a similar or decreased infectivity when compared to control viruses (see Table 2, provided below). Furthermore, Shankara may suggest that subgroup D adenovirus are better than subgroup C viruses at infecting dendritic cells, but one of skill in the art would not have extrapolated such a statement to predict that the infectivity of chimeric adenoviruses in view of the results shown in Table 2. Applicants also argue that one of skill in the art in view of Shankara, Dechecchi et al. and Huang et al. would not have been motivated to select the specifically claimed subgroup D adenoviruses that exhibit enhanced infectivity to arrive at the claimed invention. Furthermore, if one of skill in the art did combine the teachings of Shankara, Dechecchi et al. and Huang et al., the resulting composition would not result in adenovirus particles since none of the cited references discuss how to select the subgroup D fibers that yield increased infectivity.

In response, Shankara produce a chimeric subgroup C adenovirus with a fiber from Adenovirus 17 (a subgroup D adenovirus). More specifically, Shankara replace the N-terminal 16 amino acids of the Ad 17 fiber with the homologous region from the Ad2 fiber (see claim 16). In addition, the only difference between the instant invention (see claims 1, 2, 3, 8, 14 and 16) and the recombinant adenovirus taught by Shankara is that the claimed subgroup D adenovirus is Ad37 and not Ad17. Furthermore, the recombinant/chimeric adenovirus of Shankara infected 90% of the dendritic cells,

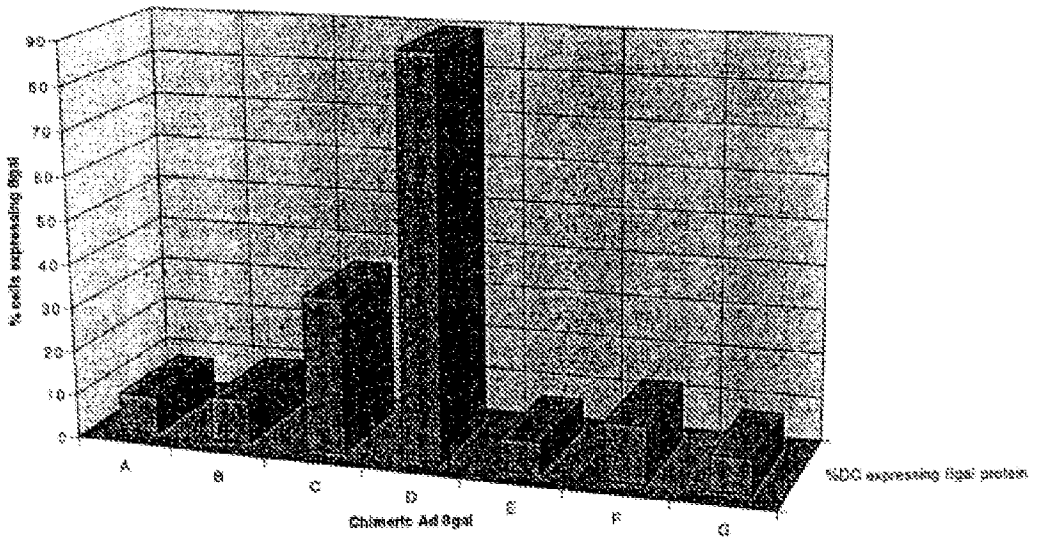
whereas the Ad2 control only infected 8.5% and the Ad5 control infected 35% of the same cell type. Therefore, one of ordinary skill in the art would have a reasonable expectation of success at generating a recombinant adenovirus (Ad5) with a chimeric fiber protein of Ad37 and Ad5 sequences, based on the recombinant Ad2/Bgal/F17 virus of Shankara that has an increased infectivity towards dendritic cells (see Table 2 and Figure 6 below).

Table 2

Ad/βgal vector	%DC expressing βgal protein as measured by X gal staining
Ad2/βgal4 (A)*	~8.5
Ad2ΔCMV/βgal (B)	~10
Ad5/βgal (C)	~35
Ad2/βgal/F17 (D)	**~90**
Ad2/βgal 5RDG HM (E)	~7.1
Ad2/βgal 17RGD HM (F)	~13
Ad2/βgal SV40nls HM (G)	~8

*letter in brackets identifies the corresponding vectors in the plot of Figure 6.

Of all the vectors tested, the chimeric adenoviral vector Ad2/βgal F17 gives rise to the significantly highest frequency of infected DC cells. All other vectors gave more or less the same percentage of transduced cells, indicating that the chimeric Ad vector with Ad17 fiber sequences infects DC very efficiently.



(New Rejection Necessitated by Amendments) Claims 1-4, 6-8, 14, 16, 25-27, 34-40 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shankara (WO 99/47180), Dechecchi et al. (Journal of Virology, 2001), Huang et al. (Journal of Virology, 1999) and Kaleko et al. (US PGPub 2003/0215948 A1).

The claimed invention is also drawn to the virus particle comprising a capsid that has a PD1 mutation of the penton protein that reduces or eliminates the binding of the penton protein to alpha V integrins.

Kaleko et al. teach the mutation of the penton protein of an adenovirus capsid that focuses on amino acids 337 to 344 of the penton protein. This mutation is referred to as PD1 and reduces the interaction of the penton protein and alpha V integrins. *See paragraph 90.*

It would have been obvious to one of ordinary skill in the art to modify the composition taught by Shankara in order to create a recombinant Ad5 with a fiber protein containing either all or a portion of the fiber protein from Ad37, thereby targeting dendritic cells and generating a recombinant adenovirus with a fiber protein that has a

reduced interaction with HSP and with a PD1 mutation to the penton protein that reduces penton interaction with the alpha V integrin. One would have been motivated to do so, given the suggestion by Shankara that Ad2 (a C adenovirus) with a fiber protein from Ad17 (a D adenovirus) increases the targeting of dendritic cells. There would have been a reasonable expectation of success, given the knowledge that adenoviruses 2 and 5 use their fiber protein to interact with cellular HSP during infection, as taught by Dechecchi et al., also given the knowledge that mutating Ad37 fiber protein in order to determine the affect mutations have on cellular tropism, as taught by Huang et al., and also given the knowledge that by performing a PD1 mutation of the penton protein, the resulting adenovirus looses it ability to readily bind to alpha V integrins. Furthermore, while Shankara and Huang et al. do not comment on reduced HSP interaction, this would have been a natural outcome of combining their teachings as outlined above, particularly in view of Dechecchi et al. In addition, the structure of the product is the same as is instantly claimed, thus any function(s) associated with the claimed structure is expected to be present in the structure of the prior art. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Objections

Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648